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Germinal centres in diagnostic biopsies of pSS patients are not a risk factor for non-Hodgkin's lymphoma but a reflection of high disease activity.

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Dear Editor,

With great interest we have read the article of Sène et al. (1) in which ectopic germinal centres (GCs) in labial gland biopsies of primary Sjögren syndrome (pSS) patients were found predictive for Non-Hodgkin's lymphoma (NHL) development later in the disease. In the univariate analysis the presence of GCs in these biopsies was not significantly different between pSS patients that developed NHL or pSS patients that did not. However, multivariate analysis revealed that presence of GCs in biopsies was an independent predictor for NHL development (1). This study adds to the ongoing discussion about the presence of ectopic GCs in pSS diagnostic salivary gland biopsies as a risk factor for subsequent NHL development. The study of Theander et al. (2) showed that GCs in diagnostic labial gland biopsies was predictive for NHL development in pSS patients, whereas we (3) and others (4,5) did not detect such an association. As discussed extensively, (3,6) a major reason for the apparent discrepancy in the different studies was the variation in NHL-subtypes that were included.

Remarkably, half of the pSS patients in the study of Sène et al. (1) were male, whereas in the other studies that evaluated the presence of GCs as risk factor, the majority of patients (>81%) were females (2–5). Whether the predictive value of presence of GCs in diagnostic biopsies differs between males and females is not known.

A very unusual observation in the study of Sène et al. (1) was that **all** pSS patients who developed NHL, had a monoclonal gammopathy (MG). In pSS patients in general, the presence of MG is 4-22% (1,7,8). We observed MG at time of lymphoma diagnosis in 4/8 (50%) pSS patients with a

parotid MALT lymphoma (Haacke et al., unpublished data). In another recent study only 3/7 (43%) pSS patients with pulmonary MALT lymphomas exhibited MG (9). Presence of MG is known as a risk factor for NHL development, but is also associated with higher disease activity (8,10). The presence of MG in pSS pre-lymphoma patients in the study of Sène et al. (1), could thus also be a reflection of high disease activity (ESSDAI) which is an independent predictor for NHL development (11).

Also the presence of GCs in biopsies is associated with high disease status (12). Since disease activity as measured by ESSDAI can change over time, (13) the time point when the diagnostic pSS biopsy is taken, is of crucial importance. If a labial gland biopsy is taken during a period of relatively low disease activity, the likelihood of presence of GCs might consequently be low. On the other hand, when a diagnostic pSS salivary gland biopsy is taken in a period of high disease activity, the chance of finding GCs is higher.

Thus, both GCs and MG are associated with higher disease status, but there is no clear indication that presence of *ectopic* GCs is a prerequisite for MALT lymphoma development. There are many pSS patients with GCs in their salivary gland biopsies that do not develop NHL. Of note, presence of GCs is usually assessed in labial salivary glands, which are not the sites where MALT lymphoma preferentially develop. We conclude that for prediction of pSS patients who are at risk for NHL development, clinical and laboratory factors such as low C4, RF-positivity, presence of cryoglobulin, highly active disease, purpura, lymphadenopathy and especially persistent parotid enlargement (5,11,14) are more important than presence of GCs in diagnostic salivary gland biopsies.

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